

CLAIMS

1. A method for treating a subject for a DTMR, comprising:
administering to said subject an effective amount of a tetracycline
5 compound, such that said DTMR is treated.
2. The method of claim 1, wherein said effective amount is effective to modulate translation of said subject's RNA.
- 10 3. The method of claim 1, wherein said effective amount is effective to modulate the half-life of said subject's RNA.
4. The method of claim 1, wherein said effective amount is effective to affect message translocation.
- 15 5. The method of claim 1, wherein said effective amount is effective to modulate the binding of proteins to said subject's RNA.
6. The method of claim 1, wherein said effective amount is effective to modulate
20 splicing of said subject's RNA.
7. The method of claim 1, wherein said subject is a plant or virus.
8. The method of claim 1, wherein said subject is an animal.
- 25 9. The method of claim 8, wherein said mammal is a human.
10. The method of claim 7, wherein the amount of at least one protein is modulated in the subject.
- 30 11. The method of claim 1, wherein the tetracycline compound is a substituted tetracycline compound.
12. A method for modulating RNA, comprising:
35 contacting RNA or a cellular component with a substituted tetracycline, such that modulation of RNA occurs.

13. The method of claim 12, wherein said modulation of RNA comprises modulation of RNA translation.

14. The method of claim 13, wherein said substituted tetracycline compound inhibits
5 said RNA translation.

15. The method of claim 14, wherein said substituted tetracycline compound inhibits said RNA translation by inhibiting initiation of translation.

10 16. The method of claim 12, wherein said substituted tetracycline compound modulates said RNA translation by altering the point at which translation terminates.

17. The method of claim 12, wherein said modulation of RNA comprises modulation of the half-life of said RNA.

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18. The method of claim 17, wherein said substituted tetracycline compound increases said half-life of said RNA.

19. The method of claim 17, wherein said substituted tetracycline compound
20 decreases the half-life of said RNA.

20. The method of claim 12, wherein said modulation of RNA comprises modulation of the translocation of said RNA.

25 21. The method of claim 12, wherein said modulation of RNA comprises modulation of interactions of said RNA with proteins.

22. The method of claim 21, wherein said substituted tetracycline compound promotes said interactions between said RNA and said proteins.

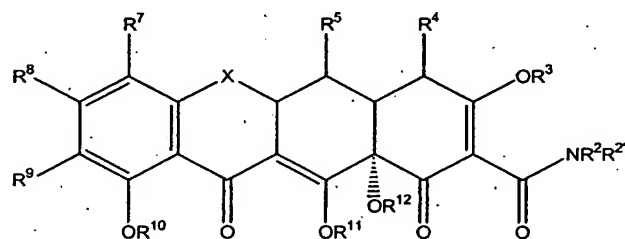
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23. The method of claim 21, wherein said substituted tetracycline compound decreases interactions between said RNA and said proteins.

24. The method of claim 21, wherein said proteins are selected from the group
35 consisting of: hnRNP proteins, snRNP proteins, ribosomal proteins, and endonucleases.

25. The method of claim 21, wherein said proteins are associated with translation.

26. The method of claim 12, wherein said modulation of RNA comprises modulation of RNA splicing.
- 5 27. The method of claim 26, wherein said substituted tetracycline compound promotes RNA splicing.
28. The method of claim 26, wherein said substituted tetracycline compound inhibits RNA splicing.
- 10 29. The method of claim 12, wherein said cellular component is a subject's cell.
30. The method of claim 12, wherein said RNA is mRNA.
- 15 31. The method of claim 12, wherein said RNA is tRNA.
32. The method of claim 12, wherein said RNA is ribosomal RNA.
33. The method of claim 12, wherein said RNA is a nuclear RNA.
- 20 34. The method of claim 12, wherein said RNA is a snRNA.
35. The method of claim 12, wherein said cellular component comprises RNA.
- 25 36. The method of claim 1, wherein said substituted tetracycline compound is of the formula (I):



(I)

wherein

- 30 $R^2, R^{2'}, R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
- $R^{2'}, R^3, R^{10}, R^{11}$ and R^{12} are each hydrogen, alkyl, alkenyl, alkynyl, substituted carbonyl, or a pro-drug moiety;

- R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, hydroxyl, halogen, or hydrogen;
 R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;
- 5 R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;
- R^7 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or $-(CH_2)_{0-3}NR^{7c}C(=W')WR^{7a}$;
- 10 R^8 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or $-(CH_2)_{0-3}NR^{8c}C(=E')ER^{8a}$;
- R^9 is hydrogen, hydroxyl, halogen, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclic, thionitroso, or $-(CH_2)_{0-3}NR^{9c}C(=Z')ZR^{9a}$;
- 15 $R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}$, and R^{8f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;
- 20 R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;
- E is $CR^{8d}R^{8e}$, S, NR^{8b} or O;
- E' is O, NR^{8f} , or S;
- 25 W is $CR^{7d}R^{7e}$, S, NR^{7b} or O;
- W' is O, NR^{7f} , or S;
- X is $CHC(R^{13}Y'Y)$, $C=CR^{13}Y$, $CR^{6'}R^6$, S, NR^6 , or O;
- Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;
- 30 Z is $CR^{9d}R^{9e}$, S, NR^{9b} or O;
- Z' is O, S, or NR^{9f} , and pharmaceutically acceptable salts, esters and enantiomers thereof.
- 35 37. The method of claim 36, wherein $R^2, R^{2'}, R^8, R^{10}, R^{11}$, and R^{12} are each hydrogen, X is $CR^6R^{6'}$, and R^4 is $NR^{4'}R^{4''}$, wherein $R^{4'}$ and $R^{4''}$ are each methyl.

38. The method of claim 37, wherein R^9 is hydrogen.
39. The method of claim 38, wherein R^7 is substituted or unsubstituted aryl.
- 5 40. The method of claim 39, wherein R^7 is substituted or unsubstituted phenyl.
41. The method of claim 40, wherein R^7 is substituted with one or more substituents.
42. The method of claim 41, wherein said substituents are each independently alkyl,
10 alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy,
alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl,
alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl,
alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino,
acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates,
15 alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido,
heterocyclyl, alkylaryl, aryl or heterocyclic moiety.
43. The method of claim 38, wherein R^7 is substituted or unsubstituted alkenyl.
- 20 44. The method of claim 37, wherein R^7 is substituted or unsubstituted heteroaryl
and R^9 is alkyl.
45. The method of claim 36, wherein R^7 is dialkylamino.
- 25 46. The method of claim 45, wherein R^9 is alkylamino.
47. The method of claim 45, wherein R^9 is $-NR^{9c}C(=Z')ZR^{9a}$, wherein R^{9c} is
hydrogen, Z' is nitrogen or oxygen, Z is NH, and R^{9a} is aryl or aralkyl.
- 30 48. A method for identifying tetracycline compounds for treating DTMR,
comprising: contacting a cellular component with a tetracycline compound; measuring
the ability of the tetracycline compound to modulate RNA, to thereby identify a
tetracycline compound for treating DTMR.
- 35 49. The method of claim 48, wherein RNA translation is measured.
50. The method of claim 48, wherein the half-life of RNA is measured.

51. The method of claim 48, wherein translocation of RNA is measured.
52. The method of claim 48, wherein the interaction of RNA with proteins is
5 measured.
53. The method of claim 48, wherein modulation of RNA splicing is measured.
54. The method of claim 1 or 48, wherein said tetracycline compound is a
10 tetracycline compound of Table 2.
55. A packaged composition, comprising a tetracycline compound and instructions
for using said tetracycline compound to treat a DTMR.
- 15 56. The packaged composition of claim 55, wherein said composition further
comprises a pharmaceutically acceptable carrier.